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Acute Respiratory Distress Syndrome (ARDS): Pathogenesis and Emerging Treatment Modalities

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Although the name acute respiratory distress syndrome (ARDS) was not established until 1967, ARDS is a condition which has been documented and, to some extent described prior to the 1900's.[1,2] Over the last century ARDS has been characterized by several names which include: shock lung, wet lung, DaNang lung, fat embolism, congestive atelectasis, oxygen toxicity, stiff lung syndrome, white lung syndrome, and pump lung, to mention a few.[1,3] A study conducted by Ashbaugh and colleagues in 1967 described the hospital course of 12 patients, including an 11-year-old child, with an acute onset of the respiratory-distress syndrome.[2] The syndrome was discernable by its symptoms of tachypnea, hypoxemia, cyanosis, decreased lung compliance, and diffuse infiltrates on chest radiograph. The 12 patients enrolled in the study were noted as being refractory to oxygen therapy and did not respond to the usual management of respiratory failure.[2] At that time Ashbaugh and colleagues established the term acute respiratory distress syndrome (ARDS) for this condition. However, a publication in 1971 utilized the term adult respiratory distress syndrome interchangeably with acute respiratory distress syndrome and the use of the heading adult has continued to persevere through the years.[4] During the last two decades the incidence of ARDS has been estimated to be as low as 1.5 to 3.5 and as high as 75 cases per a 100,000 population per year.[6,7] This wide range of incidence is partly due to differing diagnostic criteria as well as the lack of consistent definitions. In 1994 the American-European Consensus Conference (AECC) on ARDS convened in order to establish a uniform definition and recommended criteria for diagnosis of acute lung injury (ALI) and ARDS in order to provide for consistency of research and incident reporting.[5] The results of the AECC not only provided a standard definition but also concluded that the condition should be referred to as acute, not adult, respiratory distress syndrome, due to its occurrence in children.[5] The term acute respiratory distress syndrome and its diagnostic criteria are not the only controversial aspects of

this condition. In addition to differing definitions and wide ranges of incident reporting, other areas of debate in ARDS include: the number and classification of the phases of ARDS, recommended diagnostic criteria, identifying markers of ARDS, the role of the advance practice nurse and treatment modalities.

The AECC defined acute lung injury (ALI) as "a syndrome of inflammation and increased permeability that is associated with a constellation of clinical, radiologic, and physiologic abnormalities that cannot be explained by, but may coexist with, left atrial or pulmonary capillary hypertension". [5(p819)] Reserving the term ARDS for the most severe cases of ALI, the AECC clarified that even though patients diagnosed with ARDS possess the recommended criteria for ALI, not all patients with ALI meet the diagnostic criteria for ARDS.[5] Suggested criteria by the AECC for diagnosing ALI include: an acute onset of the syndrome, frontal chest radiograph with bilateral infiltrates, a pulmonary wedge pressure less than 18 millimeters of mercury (mm Hg) or no signs of left atrial hypertension, and a partial pressure of arterial oxygen to inspired oxygen ratio (PaO_2/FiO_2) less than 300 mm Hg. Diagnostic criteria for ARDS is the same, with the exception of a PaO_2/FiO_2 being less than 200 mm Hg, versus 300 mm Hg for ALI.[5] Although ARDS is seen as having an acute onset it is the result of an initial source of injury, which ultimately causes an inflammatory process in the lung.

The acute respiratory distress syndrome is a complex condition. It is often preceded by a critical illness leading to injury of the lung.[8] The lung injury can be either direct (pulmonary), or indirect (extrapulmonary). Sources of direct injury include: pneumonia, aspiration, near drowning, toxic inhalation, and pulmonary contusion. Indirect sources of injury are severe trauma (not involving the lung), multiple transfusions, acute pancreatitis, drug overdose, and sepsis[9], which is a reported cause of ARDS in 40 percent of patients.[10] Since ARDS is a syndrome that develops as a result of a direct or indirect injury to the lung, diagnosis and effective treatment are vital to patient survival and recovery.

Pathophysiology of ARDS

The syndrome of acute respiratory distress is an inflammatory process caused by direct or indirect injury to the alveoli of the lungs.[9,11] Injury to the alveolar epithelium and capillary endothelium initiates the inflammatory process, causing increased alveolar permeability, degradation of surfactant, and impaired gas exchange. The alveolar epithelium is composed of two types of cells. Flat type I cells make up 90 percent of the alveolar epithelium, while the remaining 10 percent are composed of cuboidal type II cells.[6] The type I alveolar cells are squamous epithelium, which are structured to promote gas exchange and inhibit fluid transudation. Only one cell layer thick, type I cells are easily injured and especially sensitive to oxygen and inhaled agents.[12] The cuboidal type II cells are more resistant to injury than the type I cells. In addition to producing surfactant and facilitating ion transport, type II cells proliferate and differentiate to type I cells.[6,12]

Surfactant has many functions in the pulmonary system. Among these functions is its importance in normal gas exchange as well as its probable activity in epithelial permeability and host defense.[13] Surfactant, which lines the alveoli, is secreted by type II epithelial cells and composed of phospholipids, and collagenous glycoproteins or hydrophobic proteins called surfactant-specific proteins (SP).[13,14] These surfactant-specific proteins are classified as SP-A, SP-B, SP-C, and SP-D.[15] SP-A is the most abundant protein in surfactant and contains collagenous glycoproteins. SP-A is produced by both type II alveolar cells and Clara cells, and plays a role in stimulating phagocytosis by alveolar macrophages and blood monocytes.[13,16] Proteins SP-B and SP-C contain hydrophobic proteins and appear to be necessary elements in surfactant replacement treatments.[13,14] SP-D, produced by lung epithelial cells, has been shown to bind to bacteria.[13] Although the significance of this binding has not been determined, it is believed that SP-D may "(a) serve as a bridge between bacteria and phagocytes and enhance binding, uptake and killing; (b) inhibit the binding of organisms to respiratory epithelium; (c) facilitate the physical clearance of bacteria; or (d) interfere with bacterial proliferation".[17(p104)] Although surfactant has many purposes, the key role of surfactant is to reduce surface tension of

the alveolar lining in the lung. Surfactant prevents the alveoli from collapsing by reducing surface tension of the alveoli, especially during expiration. Surfactant improves lung compliance, making it easier to expand the lungs, and decrease the effort associated with breathing.[12,14] Receptors in the respiratory tract are another element in the pulmonary system, which assist our respiratory efforts. [12,13,14]

The receptors in the tracheobronchial tree and the alveoli have two main functions. These functions include: regulation of the pattern of breathing in response to physiological changes, and to cause changes in the patterns of breathing in order to serve as a protective mechanism against the incursion of destructive substances into the pulmonary system.[18] Juxta-pulmonary capillary receptors, referred to as J-receptors, are located close to the alveoli, lying near capillaries in the alveolar septa.[12,19] At this location, the J-receptors are easily reached by gases as well as the pulmonary circulation.[19] J-receptors are innervated by the vagus nerve and become stimulated with a rise in interstitial volume.[12,19] Pulmonary congestion, such as fluid in the alveoli or distention of pulmonary capillaries, causes an increase in pulmonary capillary pressure leading to stimulation of the J-receptors. The greater the congestion, the more intense the excitation of the endings of the J-receptors.[19] Stimulation of these J-receptors can lead to the sensation of dyspnea and have been shown to produce reflex bradycardia and apnea, which is then followed by rapid shallow breathing.[12,18,19,20]

Phases of ARDS

Consistent with the discrepancies in definitions and diagnosing criteria for ARDS, there have also been different descriptions in the criteria for phasing ARDS. Current research divides ARDS into three phases (Table 1), which may overlap or be omitted altogether.[11]

Acute Phase

The acute phase, also identified as the exudative phase, is often clinically evident within hours of the injury.[1,11] According to Hudson and Steinberg 50 percent of patients who develop ARDS, do so within 24 hours of the initial injury, with an additional 35 percent of patients at risk for developing ARDS within 72 hours.[21] The remaining 15 percent of patients who progress to

ARDS do so within the next several days.[21] Clinical manifestations of ARDS include severe dyspnea, tachypnea, dry cough with retrosternal discomfort, hypoxemia refractory to oxygen therapy, decreased lung compliance, and diffuse infiltrates on frontal chest X-ray.[1,2]

Direct or indirect injury to the alveolar epithelium and capillary endothelium, causes these membranes to lose their integrity, permitting protein-rich fluid to enter alveolar spaces, and consequently impairing gas exchange (Figure 1).[10] Direct injury to the lungs disrupts the tight junctions between the alveolar cells, allowing transudation of fluid into the alveolus.[1] With indirect injury to the lungs, such as in sepsis, the endothelial cells become rounded. This rounded shape of the endothelial cells opens up the tight junctions allowing plasma to leak into the interstitial space and progress into the alveolus.[1] Alveolocapillary damage activates a massive inflammatory process in the lungs, leading to sequestration of neutrophils, involvement of the complement system, stimulation of platelet aggregation, and production of microthrombi.[1,22,23] In turn platelets release neutrophil chemotactic factors, which trigger the sequestration and aggregation of neutrophils and the release of even more mediators.[22] These mediators produce extensive alveolocapillary membrane damage further increasing membrane permeability, airway constriction, and activation of additional inflammatory cells.[24] Increased permeability allows fluid, protein, and blood cells to enter the alveoli. The resulting pulmonary edema leads to decreased lung compliance and impaired gas exchange.[22] Damage to the epithelial cells not only causes increased membrane permeability, but also the loss of type II cells. Without type II cells fluid and ion transport is disrupted inhibiting the removal of edema from the alveoli. Another consequence of damage to the type II cells is the interruption of surfactant production.[6] As the levels of surfactant decrease, compliance is impaired and the risk of atelectasis is intensified. The damaged lung is now poorly ventilated and hypoxic vasoconstriction develops, causing a right-to-left shunt.[1,22]

Neutrophils. The role of neutrophils in acute respiratory distress syndrome has been the focus of several studies.[16,25,26,27] Bronchoalveolar lavage (BAL) has been performed on ARDS patients in order to obtain samples from the lower respiratory tract, which are then studied to analyze the

components involved in the inflammatory response.[25] Baughman et al. studied two sets of bronchoalveolar lavage fluid (BALF) samples in sepsis-related ARDS patients. The initial sample was taken within 48 hours of the onset of ARDS, and the second sample four days after initiation of treatment. The initial BALF sample showed no difference in neutrophil counts for survivors versus nonsurvivors.[25] However, in the second sample, it was discovered that with the exception of one patient, there was a decrease of greater than five percent in the neutrophil count of the patients who survived 30 days, while the count either stayed the same or increased in those patients who had died. Baughman and colleagues concluded that the decline of neutrophils in the BALF was linked with a better prognosis for patients with sepsis-associated ARDS.[25]

Consistent with other studies, Geerts et al. concurred that a higher number of neutrophils and their degranulation products (elastase and lactoferrin) were found in the BALF samples of patients with ARDS as compared to patients at risk for ARDS.[26] In addition they proposed that the amount of neutrophils found in ARDS patients is associated with impairment in gas exchange as well as abnormalities in lung protein permeability. Even though they agreed neutrophils were to blame for the tissue injury of these patients, Geerts and colleagues hypothesized that the reduction of natural inhibitors of the inflammatory process also plays a fundamental role in the progression of ARDS.[26] In addition to distinguishing the amount of neutrophils in the BALF, Geerts and colleagues sought to identify anti-inflammatory mediators, specifically the Clara cell 16-kD protein (CC16).[26] CC16, a natural inhibitor of INF- γ, is of great interest to researchers searching for a treatment of ARDS.[27] Although its role is not completely understood, CC16 is thought to have lung protective properties by means of its immune suppressive action. By interfering with the cytokine network, CC16 is able to cause inhibition of the inflammatory process. In the study by Dierynck et al., CC16 was found to be an inhibitor of interferon-γ (IFN- γ), either by inhibiting its effects or blocking the production of IFN- γ by interleukin-2. Interferon-γ has many functions, including antiviral activity, as well as its ability to activate macrophages which triggers neutrophil chemotaxis, leading to inflammation and stimulation of phagocytosis.[27] While the average amount of CC16 found in ARDS and at-risk

patients was not found to be significantly different, it was determined that CC16 has lung protective effects through its immunosuppressive role.[26,27] Even though there was no correlation between CC16 and neutrophil influx, a correlation between increased levels of CC16 and higher PaO_2/FIO_2 ratios was determined.[26]

In agreement with the above studies, research by Baker et al. concluded that a massive invasion of activated neutrophils, which damage capillary endothelium and alveolar epithelium, leads to alveolar edema and surfactant dysfunction.[16] In their study, all 18 patients had an elevated number of neutrophils in their bronchoalveolar lavage fluid samples. Taking their study one step further, they examined the effects of neutrophil degranulation products on surfactant. Their findings concluded that the elastase, a degranulation product from the activated neutrophils, causes direct damage to SP-A. Damage to SP-A, edema in the alveoli, and impairment of the type II cells all participate in the inactivation and inhibition of surfactant. With attentuation of functioning surfactant the alveoli are prone to collapse, increasing lung compliance and work of breathing.[16]

Cytokines. Cytokines are chemical messengers, which carry signals between cells in the immune system, resulting in modification of the function of target cell performance.[23] Binding of the cytokine to a receptor on the target cell leads to initiation of a message within the target cell, producing a functional response.[23] Cytokines may be produced locally in the epithelial cells of the lung, lung inflammatory cells, fibroblasts, or by extrapulmonary factors (e.g., sepsis, acute pancreatitis).[6] Cytokines, termed monokines when produced from monocytes or macrophages, and other proinflammatory complexes work to initiate and intensify the inflammatory response in acute respiratory distress syndrome .[23]

Proinflammatory cytokines, specifically tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6), and interleukin-8 (IL-8), a strong neutrophil chemotaxin and activator,[28] have been found to stimulate or trigger certain neutrophil functions.[29] Tumor necrosis factor (TNF) is secreted from macrophages in response to gram-negative and gram-positive bacteria, cytokines, and other stimuli.[23] Following TNF infusion in animals neutrophils sequester in the lung, intravascular

coagulation is generated through the inhibition of protein C and the release of endothelium-derived procoagulants, as well as hemorrhage and edema of essential organs such as the kidneys, intestines and lungs. [23]Chollet-Martin and colleagues, studied the blood and bronchoalveolar fluid of 29 patients in order to determine the relationship between the level of cytokines and neutrophils. TNF-α, IL-6 and IL-8 levels were increased in all of the tested patients, with significantly higher values found in the ARDS groups. Results of the study concluded that neutrophils from both blood and alveoli are involved in the ARDS process. It was also determined that the increased level of cytokines, TNF-α, IL-6 and IL-8, perpetuated neutrophil hyperactivity and triggered selected roles of the neutrophils.[29] Although the measurement of these cytokines in BALF has not been found to be predictive of ARDS, Donnelly et al. discovered higher levels of IL-8 in at-risk patients who went on to develop ARDS when compared to at-risk patients who did not progress to ARDS.[30] Those patients who survive the acute phase of ARDS but do not reach resolution of the disorder progress to the next stage of the syndrome.

Chronic Phase

If recovery or death does not occur within the first few days, ARDS patients advance to the chronic phase. The chronic phase of ARDS, also termed the proliferative or fibroproliferative phase, occurs seven to ten days after the initial injury, and may persist up to a month after the injury.[1,11] During this phase, pulmonary edema is partially resolved. Impaired gas exchange and increased airway pressures remain, further impairing lung compliance.[11] Fibroblast proliferation occurs, which leads to collagen deposits in the alveolar air spaces and interstitium, thus thickening the alveoli and interstitial space.[1,11] The accumulation of fibrin may be the result of an imbalance in the levels of coagulant activity and fibrinolytic activity in the lower airways and blood vessel walls.[31,32] An increase in function of the coagulation system and a decrease in the functioning of fibrinolysis may lead to fibrin deposits, the resolution of which is dependent on the balance between these two systems.[32] The resulting fibrosis gradually diminishes functioning alveoli, bronchioles and interstitium, leading to further impaired ventilation, decreased

compliance, and a greater right-to-left shunt.[22] In patients who do not survive, the fibroproliferative phase continues[31] while the survivors progress into the recovery phase.

Recovery Phase

The recovery phase may begin within the first few days of injury or during resolution of the chronic phase. During the recovery phase fibrosis and hypoxemia begin to resolve, fluid and proteins are transported out of the alveoli and compliance improves.[11] "In survivors, resolution of the fibroproliferative changes occurs, along with repopulation of the air-lung interface by Type II epithelial cells, repopulation of the blood-lung interface with microvascular endothelial cells, and restoration of the extracellular matrix".[31(p199)] Type II cells proliferate and differentiate into type I cells, reestablishing the alveolar epithelium, which inhibits fluid transudation and promotes gas exchange.[6] Type II cells initiate production of surfactant and ion transport, to include active sodium uptake, which facilitates the removal of alveolar fluid.[33]

In 1994 McHugh et al. studied the results of pulmonary function tests (PFTs) of ARDS survivors at predetermined time intervals.[34] In their study patients' PFTs recorded at two weeks post extubation continued to show significant restrictive impairments. At the three and six month intervals, substantial improvement in the PFT results had occurred; however, no further improvement was noted one year after extubation. It was determined that patients who survive ARDS return to near normal respiratory function within six months of initial injury. Pulmonary function of these patients ranged from normal and mild restrictive impairments to severe impairments. It was determined that the severity of the restrictive impairments correlated with the intensity of the illness and duration of mechanical ventilation.[34]

Treatment Modalities

Treatment of acute respiratory distress syndrome is considered supportive, and must focus on diagnosis and resolution of the underlying cause of injury.[1,11] "Studies continually seek to pinpoint the best combination of ventilation modes, airway pressures, and fluid management methods that will promote healing without further injuring tissue".[11(p26)] Better understanding of the pathogenesis of ARDS has led to the research of several treatment modalities. Various modes

of ventilation, fluid management, liquid ventilation, prone positioning, continuous rotation, and administration of nitric oxide and surfactant, are some of the treatment modalities used and being studied.[6]

In the 1970's high tidal volumes, ranging from 10 to 15 milliliters per kilogram body weight, were recommended for treatment of ARDS.[8] In order to prevent over distention and volutrauma of the alveoli, treatment has recently been focused on regulating inspiratory pressures. Regulation of inspiratory pressures results in fluctuating tidal volumes, which are smaller and more consistent with resting volumes, normally five to seven milliliters per kilogram.[6,11] The use of positive end expiratory pressure (PEEP) has also been shown to improve oxygenation and decrease mortality rates of ARDS patients.[1,2,4] Other methods of ventilation that have been studied include: high frequency ventilation, nitric oxide, liquid ventilation, and the use of extracorporeal gas exchange.[1]

Another supportive measure in the battle against ARDS is the management of fluids and hemodynamic status. One recommended clinical strategy of fluid management is gradual dehydration, which is designed to aid in the reduction of alveolar edema and accelerate its resolution.[6] When implementing this treatment plan, either through the use of diuretics, hemodialysis or ultrafiltration,[35] clinicians must assess the patient's underlying condition. While assessing and treating the primary disorder, the clinician must also carefully monitor the fluid status of patients with ALI or ARDS, ensuring adequate perfusion and oxygenation of vital organs is maintained through the use of crystalloids, blood products, vasopressors and/or colloid solutions.[24,35] For sepsis related ARDS prudent use of crystalloid fluid administration, with colloid solutions considered in hypo-oncotic patients is reccommended.[36] The use of vasopressors should be considered if the hemodynamic stability of the patient is compromised and not able to be maintained by fluids alone.[6,35]

As early as the 1970's prone positioning has demonstrated improvement in the ventilation and oxygenation of patients diagnosed with ARDS.[37] Several theories explaining the positive effects of prone positioning have been suggested, the latest of these being the ventilation

theory.[38] Studies by Mutoh et al. and Wiener et al. of prone positioning were shown to increase negative pleural pressures, which opened previously closed airways, decreased shunt and increased alveolar perfusion to dorsal lung regions.[39,40] Thus, the physiology of the ventilation theory proposes that a greater negative pleural pressure, produced by placement in the prone position, creates an adequate amount of pressure to minimize closing of the airways, resulting in lung recruitment. [39,40] Recent studies continue to show improvement in PaO_2 levels of ARDS patients placed in the prone position.[41,42,43] Although several studies have shown the positive effects of prone positioning, it is still not commonly used. Further studies which need to be pursued include: additional research on the optimal time interval for patients to remain prone, the best technique for placing patients in the prone position and studies examining the hesitancy of healthcare professionals in using the prone position.

Since acute respiratory distress syndrome is a result of the inflammatory process, the use of numerous pharmacologic therapies, which alter this process through its pathways, have been studied and utilized in the treatment of ARDS.[1,6] Glucocorticoids have been used as a treatment for ARDS because of their influence on inflammation. Glucocorticoids hinder the inflammatory pathway, suppress the synthesis of phospholipase A_2 and decrease the production of platelet-activating factor.[44] While glucocorticoids given in high doses over a short course have not shown to be effective, a study by Meduri has provided support for their prolonged administration.[44] Other pharmacologic treatment modalities include: surfactant therapy, anticytokines, antioxidants, and prostaglandin E_1; however, larger studies need to be conducted in order to establish the specific effects of these agents on patients with ARDS.[10,31]

Role of the Advanced Practice Nurse

As a healthcare provider and clinical expert, education and research are areas in which the advanced practice nurse (APN) must play a role in the recognition and treatment of ARDS. Early recognition and judicious treatment of ARDS is crucial in achieving a successful recovery. As an educator, the APN is responsible for ensuring nurses possess basic knowledge of the precursors and pathology of ARDS so diagnosis and supportive therapy may be initiated early. It

is essential that the APN remain current with research and become involved in research studies. Remaining current in the literature and familiar with ongoing studies in ARDS will allow the APN to recognize therapies and supportive measures which may assist ARDS patients in their recovery, decreasing mortality and morbidity. As a researcher, the APN is able to share the nursing perspective and his or her expertise with other professionals. Involvement in research allows the advanced practice nurse to advocate not only for the patients but also for the profession of nursing.

Summary

ARDS is a syndrome that has complicated the healing process and treatment strategies of critically ill patients for decades. Defined as diffuse pulmonary infiltrates, hypoxemia refractory to oxygen therapy, cyanosis, tachypnea, decreased lung compliance, and a PaO_2/FIO_2 ratio less than 200 mm Hg not caused by left atrial or pulmonary hypertension[2,5], acute respiratory distress syndrome is characterized as an inflammatory process preceded by direct or indirect injury to the lungs.[9,11] While ARDS is a complex syndrome, substantial progress has been made concerning the understanding of the physiological and pathophysiological processes involved.[6,31] Over the past 30 years, researchers have identified the roles of neutrophils, their degranulation products, cytokines, and inflammatory mediators in the development of acute respiratory distress syndrome. As research into the precursors of ARDS and pathophysiological processes of ARDS continues to grow,[32,45] we are able to refine current therapies and watch new treatment modalities emerge. "Although progress in specific treatments has lagged behind basic research" new understanding of the inflammatory response has sparked research in promising areas of ventilator and pharmacologic therapy.[6(p1346)] As healthcare professionals it is the duty of APNs and other providers to maintain an ongoing understanding of the pathogenesis of ARDS as well as the effectiveness of supportive therapies. Healthcare providers knowledgeable in the pathogenesis and treatment modalities of ARDS will improve the management of their critically ill patients, increasing the rate of recovery and survival.[31]

Key Points

The acute respiratory distress syndrome is a complex condition, which is often preceded by another critical illness such as sepsis, shock, trauma, multiple blood transfusions or aspiration.[8] Damage to the lung can be either direct (pulmonary) injury or indirect (extrapulmonary) injury.[9] Sources of direct injury include: pneumonia, aspiration, near drowning, toxic inhalation and pulmonary contusion. Indirect sources of injury consist of the following: severe trauma (not involving the lung), multiple transfusions, acute pancreatitis, drug overdose and sepsis.[9] Martin and McCarthy (2001) report that up to 40 percent of sepsis patients will progress to ARDS. Current research divides ARDS into three phases, which may overlap or be omitted altogether.[11] The acute phase, also called the exudative phase, may be clinically evident within 12 hours of injury.[11] The chronic phase of ARDS, also termed the proliferative or fibroproliferative phase, occurs seven to ten days after the initial injury, and may persist up to a month after the injury.[1,11] The recovery phase may begin within the first few days of injury or during resolution of the chronic phase. During the recovery phase fibrosis and hypoxemia begin to resolve, fluid and proteins are transported out of the alveoli and compliance improves.[6,11] Since ARDS is a syndrome that develops in addition to another serious illness, effective and timely treatment is vital to patient recovery and survival.

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Table 1 Phases of ARDS[1,2,6,11,33]

Acute	Chronic	Recovery
Hours-First Few Days	7-10 days	Post Chronic
Dyspnea	Pulomanary edema	Resolving fibrosis
Tachypnea	partially resolved	Resolving hypoxemia
Dry cough	Improved gas exchange	Fluid/protein exit alveoli
Hypoxemia	Increased airway pressures	Proliferation/differentiation
Decreased compliance	Decreased compliance	of type II cells
Diffuse infiltrates on x-ray		-Surfactant production
		-Ion transport

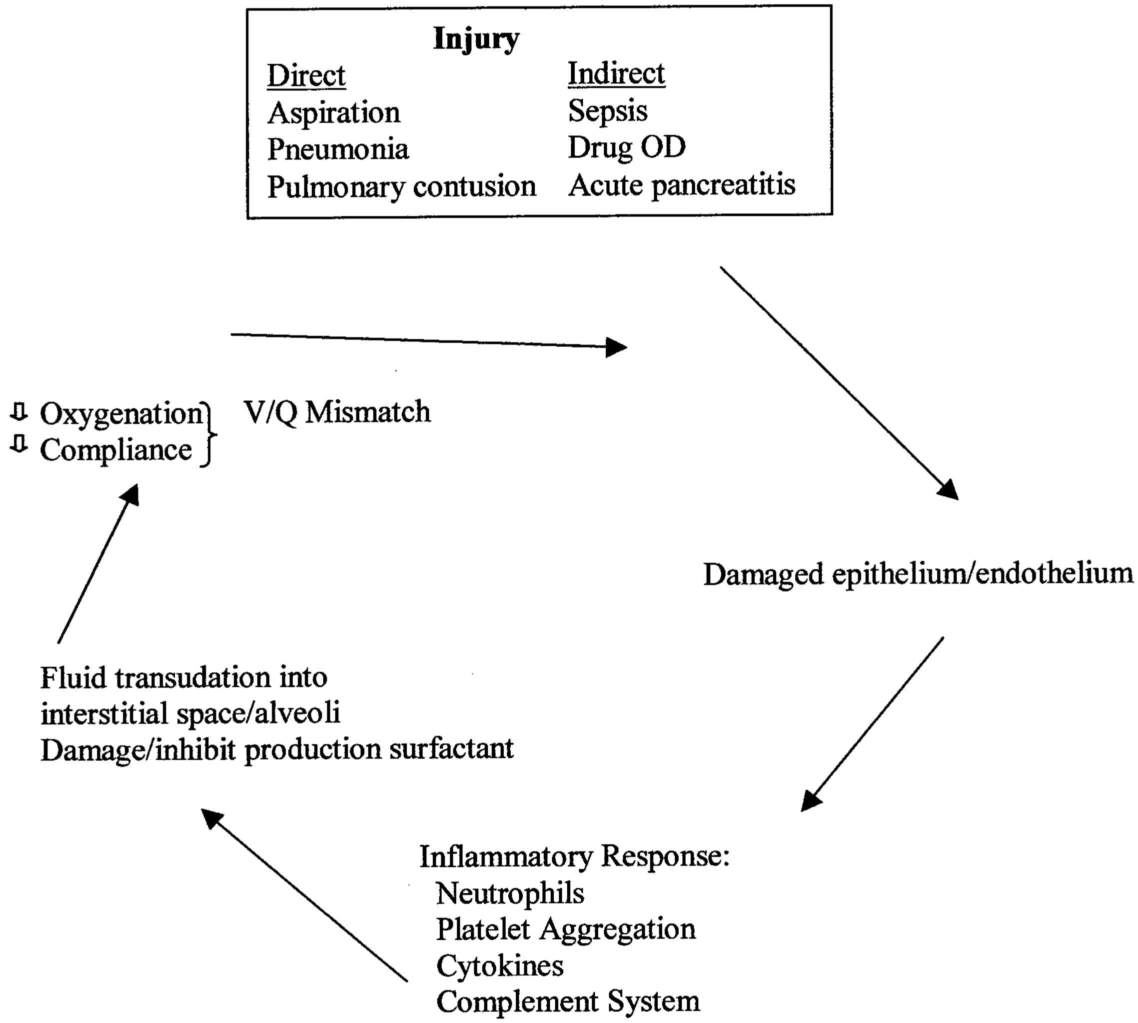

Figure 1 ARDS Progression[1,6,9,11]